Antibiotics for lower respiratory tract infection in children presenting in primary care: ARTIC-PC RCT

Paul Little,[1*] Nick A Francis,[1] Beth Stuart,[1] Gilly O'Reilly,[1] Natalie Thompson,[1] Taeko Becque,[1] Alastair D Hay,[2] Kay Wang,[3] Michael Sharland,[4] Anthony Harnden,[3] Guiqing Yao,[5] James Raftery,[1] Shihua Zhu,[1] Joseph Little,[1] Charlotte Hookham,[1] Kate Rowley,[2] Joanne Euden,[6] Kim Harman,[1] Samuel Coenen,[7] Robert C Read,[8,9] Catherine Woods,[1] Christopher C Butler,[3] Saul N Faust,[8,9] Geraldine Leydon,[1] Mandy Wan,[10] Kerenza Hood,[6] Jane Whitehurst,[11] Samantha Richards-Hall,[12] Peter Smith,[13] Michael Thomas,[1] Michael Moore[1] and Theo Verheij[1,14]

[1]Primary Care Population Sciences and Medical Education Unit, University of Southampton, Southampton, UK
[2]Centre for Academic Primary Care, Bristol Medical School, Population Health Sciences, University of Bristol, Bristol, UK
[3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[4]Institute of Infection and Immunity, St George's University, London, UK
[5]Biostatistics Research Group, Department of Health Sciences, College of Life Sciences, University of Leicester, Leicester, UK
[6]Centre for Trials Research, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK
[7]Department of Family Medicine & Population Health and Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium
[8]National Institute for Health and Care Research (NIHR) Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[9]Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK
[10]Evelina Pharmacy, Guy's and St Thomas' NHS Foundation Trust, London, UK
[11]National Institute for Health and Care Research (NIHR) Applied Research Collaboration West Midlands, Coventry, UK

[12]Southampton Primary Care Research Centre, Primary Care Population Sciences and Medical Education Unit, University of Southampton, Southampton, UK
[13]Southampton Statistical Sciences Research Institute, University of Southampton, Southampton, UK
[14]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands

*Corresponding author p.little@soton.ac.uk

Declared competing interests of authors: Theo Verheij reports grants from the European Union and The Netherlands Organisation for Health Research and Development during the conduct of the study, and grants from Abbott Laboratories (Chicago, IL, USA), Becton, Dickinson and Company (Franklin Lakes, NJ, USA), bioMérieux (Marcy-l'Étoile, France) and Janssen Pharmaceuticals (Beerse, Belgium) outside the submitted work. Paul Little was a member of the National Institute for Health and Care Research (NIHR) Journals Library Board (2011–17). Kerenza Hood is a member of the NIHR Health Technology Assessment (HTA) General Committee and the HTA Funding Strategy Group. Saul N Faust is a member of the RECOVERY Trial Steering Committee, the HTA Commissioning Board and other NIHR national groups, and reports funds to his institution but no personal payments for multiple commercial contracts, advisory board participation and presentations [Pfizer (New York, NY, USA), AstraZeneca (Cambridge, UK), MedImmune (Gaithersburg, MD, USA), Sanofi (Paris, France), CSL Seqirus (Maidenhead, UK) and Merck Group (Darmstadt, Germany)]. Robert C Read reports that he is NIHR Biomedical Research Centre Director and editor-in-chief of *Journal of Infection*. James Raftery reports membership of the NIHR HTA and Efficacy and Mechanism Evaluation Editorial Board in a paid role. Nick A Francis reports a research grant from Synairgen plc (Southampton, UK) for COVID-19 research, non-financial support for a NIHR HTA trial on reducing antibiotics for COPD from Abbott Laboratories, a speaker's fee from Abbott Laboratories, and stock/stock options from Abbott Laboratories and Synairgen plc.

Published June 2023
DOI: 10.3310/DGBV3199

Scientific summary

Antibiotics for lower respiratory tract infection in children presenting in primary care: ARTIC-PC RCT

Health Technology Assessment 2023; Vol. 27: No. 9
DOI: 10.3310/DGBV3199

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Antimicrobial resistance (AMR) is a global public health threat. Antibiotics are very commonly prescribed for children presenting with uncomplicated lower respiratory tract infection, but there is little randomised evidence of the effectiveness of antibiotics for treating these, either overall or among key clinical subgroups.

Objective

The objective was to undertake a trial of antibiotics for children presenting with lower respiratory tract infection in primary care, with a parallel observational study.

Aims

The aims were to:

1. estimate the effectiveness of amoxicillin overall and in key clinical subgroups of children presenting with uncomplicated (non-pneumonic) lower respiratory tract infection in primary care
2. estimate the cost-effectiveness of antibiotics overall in children presenting with uncomplicated (non-pneumonic) lower respiratory tract infection in primary care
3. explore the estimates of effectiveness according to key pathophysiological subgroups (the presence of bacterial pathogens)
4. explore which variables predict poor prognosis and develop a prediction model for poor prognosis
5. explore the views of parents and clinicians regarding management of children and participation in the trial.

Design

This was a placebo-controlled trial with qualitative research and health economic analysis, and a parallel observational cohort.

Setting

UK general practices.

Participants

Participants were children aged between 6 months and 12 years presenting to primary care with an acute lower respiratory tract infection, defined as one in which an acute cough is the predominant symptom and judged by the general practitioner (GP) to be infective in origin, lasting < 21 days, and with other symptoms or signs localising to the lower respiratory tract (shortness of breath, sputum, pain), and in whom pneumonia was not suspected clinically.

Outcomes

The primary outcome was the duration in days of symptoms rated moderately bad or worse (measured using a validated diary). The secondary outcomes were symptom severity on days 2–4 (0 = no problem to 6 = as bad as it could be); symptom duration until very little/no problem; reconsultations for new or worsening symptoms; progression of illness sufficient to require hospital assessment; side effects; and resource use.

Ethics

The protocol was approved by the South West – Central Bristol Research Ethics Committee (reference 15/SW/0300).

Methods

Children were randomised to receive 50 mg/kg/day oral amoxicillin in divided doses for 7 days, or placebo, using pre-prepared packs randomised by an independent statistician using computer-generated random numbers. Children whom clinicians were unwilling to randomise or parents who were unwilling for their child to be randomised were invited to participate in an observational study in which the same data as in the trial were collected.

The revised target sample size (agreed with the Trial Steering Committee, the Data Monitoring and Ethics Committee and the funder) to detect an important clinical difference of 3 days in symptoms duration was 298 participants for 80% power and 398 participants for 90% power.

Semistructured interviews were used to explore the views of management and the decisions to participate in the trial. Parents were purposefully sampled by whether they took part in the trial or the observational study, and by practice. Clinicians who recruited participants into the study were also invited to take part in a telephone interview. The interviews were analysed using thematic analysis.

Throat swabs were analysed for the presence of bacteria and viruses by multiplex polymerase chain reaction.

Statistical analysis

Cox regression was used for the primary outcome and for total symptom duration, adjusting for age, baseline symptom severity, prior duration of illness and comorbidity. Linear regression was used for symptom severity, and logistic regression was used for reconsultation, progression of illness and side effects, adjusting for the same baseline covariates as in the primary analysis. Analysis was by intention to treat, as randomised regardless of non-adherence or protocol deviations. Multiple imputation was used as the primary analysis, comprising all variables from the analysis model and any predictors of missingness, and using 100 imputations. Prespecified subgroup analyses were carried out on chest signs, sputum/rattly chest, history of fever, physician rating of unwell, shortness of breath, oxygen saturation below 95%, and STARWAVe clinical prediction rule for hospitalisation. For the observational data set, stratification by propensity scores was used to control for confounding by indication, and the data were merged with the trial data set to facilitate more powerful analyses. A logistic regression model was built to predict the progression of illness, and discrimination was assessed using estimates of area under the receiver operator curve that were bootstrapped for internal validation.

Health economic analysis

Both cost-effectiveness (in GBP per unit of primary outcome) and cost per quality-adjusted life-year (QALY) were estimated. The base case took an NHS perspective, but some non-NHS costs were also included (remedies and time off work). Resource use data were collected by a notes review in primary

care supplemented by the diary. Unit costs of primary care consultation, community services, outpatient visits and accident and emergency attendances were costed based on the Personal Social Services Research Unit. National reference costs were used to cost hospital stay based on corresponding diagnostic categories. Medications were priced based on the *British National Formulary*. All costs were based on 2019 prices. QALYs were based on the EQ-5D-Y (EuroQol-5 Dimensions Youth), collected weekly, and on the recommended national tariff.

Trial results

A total of 432 children were randomised (antibiotics, *n* = 221; placebo, *n* = 211). The duration of moderately bad symptoms was similar in the two groups [median 5 vs. 6 days, respectively; hazard ratio (HR) 1.13, 95% confidence interval (CI) 0.90 to 1.42]. Return with new or worsening symptoms (29.7% vs. 38.2%; risk ratio 0.80, 95% CI 0.58 to 1.05), progression of illness requiring hospital assessment (2.4% vs 2.0%) and side effects (38% vs. 34%) were also similar in the two groups. A small difference in mean symptom severity on days 2–4 (1.8 vs. 2.1 points; difference 0.28 points, 95% CI 0.04 to 0.51) is unlikely to be clinically meaningful. No differences were seen for the primary outcome in the five prespecified clinical subgroups in which antibiotic prescribing is common: chest signs subgroup (antibiotics 6 days vs. placebo 6 days; HR 0.97, 95% CI 0.65 to 1.43), sputum/rattly chest (5 vs. 7 days; 1.16, 95% CI 0.83 to 1.64), fever (5 vs. 6 days; 1.23, 95% CI 0.88 to 1.73), physician rating of unwell (5 vs. 6 days; 1.25, 95% CI 0.85 to 1.83) and shortness of breath (5 vs. 6 days; 1.13, 95% CI 0.72 to 1.77). There was also no evidence that the presence of bacteria in the throat swab mediated antibiotic effectiveness. Estimates from complete cases (*n* = 317) were very similar, as were estimates from a per-protocol analysis for children taking 11 or more of the of 15 doses in the first 5 days. NHS costs per child were slightly higher with antibiotics (antibiotic, £29; placebo, £26) and non-NHS costs were the same (antibiotics, £33; placebo, £33), but QALY data were too incomplete for robust imputation. The incremental cost per QALY (incremental cost-effectiveness ratio) was £30,851 (95% CI −£73,639 to £109,429) based on estimates from the means of complete cases and £6417 (95% CI −£12,240 to £20,535) based on the estimates using imputed data.

Observational study

A total of 326 children were recruited to the observational study. The estimate of benefit of antibiotics for the primary outcome was similar to that in the trial (HR 1.16, 95% CI 0.95 to 1.41). A prognostic model to predict the progression of illness consisting of seven variables (baseline severity, difference in respiratory rate from normal for age, duration of prior illness, oxygen saturation, sputum/rattly chest, passing urine less often and diarrhoea) had good discrimination (bootstrapped area under the receiver operator curve 0.85) and calibration, and a three-item model (respiratory rate, oxygen saturation, sputum/rattly chest) also performed well (area under the receiver operator curve 0.81).

Qualitative results

Thirty semistructured telephone interviews were conducted with 16 parents and 14 clinicians. Parents found it difficult to interpret the symptoms and signs, and commonly used the sounds of the cough to judge severity, which highlights the need to provide better information to support parents. Many parents said that the main reason for consulting was to receive a clinical examination and reassurance regarding illness severity. Parents acknowledged that antibiotics should be used only when 'necessary', and many of the clinicians also noted a shift in parents' expectations about antibiotics and that they were satisfied with a clinical assessment, reassurance and advice. Decisions to take part in the trial were influenced by the perceived risks associated with taking a placebo compared with immediate antibiotics, and with taking antibiotics unnecessarily. Clear communication about the self-management of their child's illness and 'safety-netting' (information on the natural course of the illness and advice about when it might be necessary to reconsult) were identified as important when implementing 'no antibiotic' prescribing strategies to reassure parents and to support prescribing decisions.

Limitations

The study was underpowered to detect small benefits in the key clinical subgroups. The trial included children who were more unwell than those in recent large generalisable cohorts, which suggests that, if anything, the benefit of antibiotics has been overestimated. Given the very large numbers of missing data, the imputed estimates in the economic analysis must be viewed with caution. If the costs of AMR were included, then these estimates of cost-effectiveness would worsen.

Conclusions

Implications for clinical care

Amoxicillin for uncomplicated chest infections in children makes little difference to symptom burden or to health or societal costs. Better access to information is needed to support parents' decision-making, as is clear clinician communication about the self-management of their child's illness and safety-netting. A prognostic score using variables that can be collected very easily during consultations can be used to identify children who are at low risk of illness progression.

Implications for future research

- The data can be incorporated in a Cochrane review and an individual patient data meta-analysis.
- Further work on the incremental QALY gain from antibiotics is needed, assessing a range of models and their implications when imputing missing QALY data, and better evidence is needed about how to incorporate AMR resource implications in modelling.
- The prognostic score should be externally validated and could be developed as an app with automated outputs, and thereafter used as a tool to reduce antibiotic prescribing for antimicrobial stewardship interventions.

Trial registration

This trial is registered as ISRCTN79914298.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 27, No. 9. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 4.014 and is ranked 27th (out of 108 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2021 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), Embase (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number XX/XX/XX. The contractual start date was in Month Year. The draft report began editorial review in Month Year and was accepted for publication in Month Year. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

Published by NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress, final files produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).